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10/812,702	03/30/2004	Choong-Chin Liew	4231/2055D	5754

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EXAMINER	
SWITZER, JULIET CAROLINE	
ART UNIT	PAPER NUMBER
1634	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/812,702	LIEW, CHOONG-CHIN	
	Examiner	Art Unit	
	Juliet C. Switzer	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 August 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *49 and 58-101* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *49 and 58-101* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/8/08 has been entered.

Claim Rejections - 35 USC § 112

1. Claims 63, 64, 65, 72, 73, 74, 81, 82, 83, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, and 101 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a rejection for new matter.

2. In claim 63, 64, 65, 72, 73, 74, 81, 82, and 83, the recitation of quantification of RNA in whole blood samples, "wherein the leukocytes thereof have not been fractionated into cell types" is new matter. Such a recitation includes, for example, testing a whole blood sample where the red blood cells and the white blood cells have been separated, and also includes, the testing of whole blood RNA. There is clearly basis for the latter, but not the former.

3. Applicant states that the office action admits that there is support for the testing of whole blood. However, the office action states that there is basis for the testing of whole blood RNA. Given the open nature of the claim language, the currently pending claims includes steps where a

whole blood sample is taken, the leukocytes are not fractionated but other portions of the blood are removed, which may or may not contain RNA. The response does not identify basis in the specification for the newly added limitation. Applicant has attempted to present a claim which excludes a particular process step from a method (that is, fractionating the leukocytes) but has not provided basis for the negative limitation. There is nothing in the specification that suggests applicant contemplated the exclusion of a step of fractionating leukocytes into cell types. Therefore, claims 63, 64, 65, 72, 73, 74, 81, 82, and 83, as well as all claims which depend from these claims are rejected for having new matter.

4. Claims 49 and 58-101 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Nature of the invention

The invention is drawn to a method for identifying a human test subject "as being a candidate for having coronary artery disease," a method of classifying a human test subject as being more likely to have coronary artery disease than to not have coronary artery disease, and methods for testing CRTAM expression.

All of the claims feature a step of quantifying a level of RNA encoded by CRTAM gene in a blood sample from a single test subject and comparing the level with a quantified level of RNA encoded by said gene in blood samples from control subjects having coronary artery disease. Some claims additionally include a comparison with a quantified level of RNA encoded

by said gene in blood samples from control subjects that are healthy control subjects and/or control subjects not having said coronary artery disease.

Some claims set forth that a determination of a statistically significant similarity between the test level and the level of control subjects having said coronary artery disease "is indicative of said coronary artery disease."

Some claims set additionally forth that a determination of a statistically difference between the test level and a quantified level of RNA from control subjects not having said coronary artery disease and significant similarity between the test level and the level of control subjects having said coronary artery disease "is indicative of said coronary artery disease."

All of the claims set forth that any findings of similarity or difference are significant at a threshold of $p<0.05$.

The nature of the invention requires the knowledge of a reliable association between comparing CRTAM expression and the indication that coronary artery disease is present in a human. Further, the practice of the invention requires an understanding of how the presence of coronary artery disease effects the level of CRTAM expression in human blood.

Amended claims 49 and 58-65 recite methods for screening human test subjects for being "a candidate" for having coronary artery disease (CAD). The use of the word "candidate" in this context suggests that the method can be used to predict if someone might develop CAD. The active process steps are identical to those in claims 66-74 and 75-83, and the lengthy "wherein clauses" are very similar or identical as well. The nature of the invention in these claims requires that a relationship is known whereby the expression of an individual's level of CTRAM predicts whether or not they will develop CAD.

All of the methods require comparing the test level with "quantified levels of RNA" from control subjects.

Scope of the claims

The claims are sufficiently broad so as to encompass detecting coronary artery disease in general, and to encompass detecting the presence of a particular type or stage of coronary artery disease. Indeed, even the claims which recite methods for detecting expression are clearly directed towards some diagnostic purpose since they set forth testing a single test subject and comparison to control populations looking for expression similarities or differences.

In addition, the "control subjects not having said coronary artery disease" encompass patients with, healthy patients and patients with some other disease, such as large granular lymphocyte leukemia.

The claims are broad in scope because they encompass that ANY level and direction of difference in gene expression between the tested subject and the healthy controls or the controls not having said coronary artery disease is indicative of said coronary artery disease, if that difference is statistically significant. That is, the claims do not set forth that one level should be higher or lower than the other, and further do not set forth how much of a "difference" between two individuals would be necessary to draw the conclusions set forth in the claims.

Claims 49 and 58-65 encompass predicting if an individual is a "candidate" for CAD. This includes methods which consider a healthy test subject and determine if they might develop CAD at some future time point.

Teachings in the Specification/Examples

Regarding coronary artery disease, the specification provides examples 9 and 21 wherein gene expression profiles of blood samples from individuals having coronary artery disease were compared with normal individuals, that is healthy patients. Example 8 teaches that 108 different genes were differentially expressed, but CRTAM was not one of these. Example 21 teaches that 967 genes were identified as being differentially expressed, and regarding the instant claims, table 3L provides a list of these genes (Example 21). CRTAM is among the genes.

The tables list genes that were differentially expressed, but does not provide any further information regarding the level of expression. For example, the tables do not teach if the expression was higher or lower in coronary artery disease patients versus controls.

The specification does not provide any guidance as to the level of "difference" that is sufficient (1 fold, 2 fold, etc) to result in a conclusion that bladder cancer is detected, nor does the specification provide any guidance as to the direction of the difference (higher or lower expression) that is expected to be observed for any single pairing of samples. The claims rely on comparisons between a test subject and the levels of quantified RNA from different types of controls, stating that particular observations of statistically significant differences or similarity between test and control can lead to different conclusions.

Regarding claims 49 and 58-65, the specification only teaches that this gene is differentially expressed in the group of patients who have CAD relative to those that are healthy controls. The specification provides no evidence to support a claim which encompasses identifying "candidates" insofar as this encompasses predicting that disease might develop.

The specification fails to provide information about an essential aspect of the invention, namely, the nature of the difference in expression that was observed between coronary artery

disease patients and healthy patients. This information is essential to understanding and practicing the claimed invention. Each of the claims requires a comparison step with "quantified levels of RNA encoded by said gene in blood samples from control subjects" yet the specification provides absolutely no guidance as to what these levels might be or how the levels of control subjects who have CAD might differ from those who are healthy controls. These levels are also not given in the prior art, particularly with regard to the control individuals who have CAD. This information is essential to understanding and practicing the claimed invention because it is critical to knowing how to interpret a particular comparison result.

State of the Prior Art and Level of Unpredictability

The expression of genes in example 21 was tested by hybridization of samples to a microarray that contains genetic information for tens of thousands of genes. This technology area is highly unpredictable, and as a result significant guidance is required to practice inventions using this type of data. Lee (Clinical Chemistry, 47:8, 1350-1352 (2001)) teaches that despite the technical accuracy of individual observations on an array, these data "are much more prone to numerous false-positive findings fundamentally because of (a) an extremely large number of observations and (b) a very wide dynamic range of gene expression values obtained from gene chip experiments." In view of these unpredictable aspects of applying such data, Lee teaches that replication is necessary to begin to screen out false positive results. There is no replication in the instant specification.

It is not known under what circumstances the result observed in the instantly examined control and test populations would be repeatable, as the results have not been validated. But even if one were to obtain the same result, it would be unknown because applicant did not

disclose the magnitude of difference in expression between coronary artery disease patients or controls, nor did applicant disclose the direction of variation. All of these inquiries are particularly important in this case since the specification is silent as to which differential expression observations would be sufficient to indicate the presence of coronary artery disease.

Further, the claims of the instant application set forth the comparison of the gene expression in a single individual versus as few as two other individuals, and they set forth that a comparing gene expression between the two is "indicative of" coronary artery disease. Neither the specification nor the claims set forth a threshold of difference between an individual's expression and the control expression of CRTAM in the blood that would be sufficient to conclude that the difference in gene expression between a test individual and any type control group is "indicative of" recited coronary artery disease. Because the claims encompass any level of altered gene expression, it is relevant to point out that the art of Cheung et al (2003) teaches that there is natural variation in gene expression among different individuals. The reference teaches an assessment of natural variation of gene expression in lymphoblastoid cells in humans, and analyzes the variation of expression data among individuals and within individuals (replicates) (p.422, last paragraph; Fig 1). The data indicates that, for example, expression of ACTG2 in 35 individuals varied by a factor of 17; and that in expression of the 40 genes with the highest variance ratios, the highest and lowest values differed by a factor of 2.4 or greater (Fig 3). It is thus unpredictable as to whether or not any level of altered gene expression is indicative of a coronary artery disease or the absence of coronary artery disease.

The unpredictability of correlating gene expression level to any phenotypic quality is taught in the post-filing art of Wu (2001). Wu teaches that gene expression data, such as

microarray data, must be interpreted in the context of other biological knowledge, involving various types of 'post genomics' informatics, including gene networks, gene pathways, and gene ontologies (p.53, left col.). The reference indicates that many factors may be influential to the outcome of data analysis, and teaches that expression data can be interpreted in many ways. The conclusions that can be drawn from a given set of data depend heavily on the particular choice of data analysis. Much of the data analysis depends on such low-level considerations as normalization and such basic assumptions as normality (p.63 - Discussion). The art of Newton et al (2001) further teaches the difficulty in applying gene expression results. Newton et al. teaches that a basic statistical problem is determining when the measured differential expression is likely to reflect a real biological shift in gene expression, and replication of data is critical to validation (p.38, third full paragraph). There is no replication of data in the instant specification.

Quantity of Experimentation

The instant specification does not provide enabling support for the practice of a single embodiment within the claimed invention. In particular, the specification does not provide adequate guidance to appraise one of ordinary skill in the art as to what levels of CRTAM gene expression must be observed to successfully conclude that coronary artery disease is indicated. Further, although the specification teaches there are differences in CRTAM levels in a coronary artery disease population versus a control patient population, the specification is silent as to the nature of the "difference" in magnitude or direction. Thus, given the lack of teaching in the specification and the highly unpredictable nature of the technology, an extensive amount of work would be required to practice the claimed invention.

In order to practice the claimed invention, one would have to undertake an extensive amount of experimentation in a highly unpredictable technology area. One would begin by trying to reproduce the results observed in the instant specification to determine if there is a relative upregulation or downregulation of CRTAM in coronary artery disease patients versus healthy control patients, as the specification does not even provide this minimal guidance. Without this knowledge one would not be able to practice the claimed invention, as the specification provides absolutely no guidance as to the control values for CRTAM expression. One would not begin to know how to interpret any results obtained in practicing the claimed methods without this baseline information. One would also, however, have to carry out this testing for validation, for it is possible that the result observed in the instant specification is intrinsic to the cohort of patients evaluated in applicant's study. Further, one would have to undertake experimentation to determine difference thresholds required to determine that a patient has or does not have a disease.

As discussed, this art area is highly unpredictable.

Conclusion

The claims include methods which encompass the detection in blood of the expression of CRTAM in a test subject and comparing this expression to control subjects, wherein the comparison itself "is indicative of coronary artery disease." The identification of gene differential expression/disease indication relationships is a highly unpredictable endeavor, requiring extensive experimentation. The specification provides minimal guidance. In light of the factors discussed, therefore, it is concluded that it would require undue experimentation to practice the claimed invention.

Response to Remarks

The rejections have been modified to address the amended claims.

The remarks point out that the amended claims neither recite, require nor even seek to encompass a method for detecting coronary artery disease in a human test subject, and that the instant claims are not the same scope as a method for detecting CAD. It is agreed that the instant claims do not recite or require methods for positively detecting CAD, but it is noted that the claims are sufficiently broad so as to encompass methods wherein the practiced method is a method of detecting CAD. For example, a method of detecting CAD which practiced the steps of claim 49 would certainly be within a broadly interpreted method of identifying an individual as being a candidate for having CAD or more likely to have CAD than not have it or simply a method for detecting and classifying expression of CTRAM. It is noted, however, that every possible embodiment of a claim does not have to be enabled for the claim to be enabled. Here other issues under 112 first paragraph for lack of enablement persist, as discussed in the rejection and in the response to remarks that follow. Furthermore, as noted in the rejection, identifying an individual as a "candidate" for disease suggests an ability of the method to predict who will develop CAD, even if it is not currently present in the test individual at the time. This suggestion is far beyond the scope of any of the disclosed data since there is no evidence that the observed differential expression would have been present PRIOR to the onset of disease.

Applicant submits on page 25 that neither the magnitude nor direction of expression of the CRTAM are absolutely required to enable the claimed invention, instead what is required is at least one method for enabling the invention, which is provided in the way of identifying

statistically significant differently expressed genes at a threshold of $p<0.05$. Applicant reiterates that the specification has discovered an association between CRTAM expression and CAD, and that the disclosure supports the instantly claimed methods. The reasons that the examiner disagrees with this assertion are set forth in the rejection. Applicant disclosed that a difference in expression was identified but failed to disclose the nature of the difference. All of the claims require comparing the level of expression with quantified levels from control subjects, but the specification provides no guidance at all as to what these levels are. Based on the teachings of the specification, one would have to begin again applicant's experimentation. Since the nature of the control values are entirely unpredictable based on applicant's disclosure, one would have to determine these values, then validate them. This is not simply routine experimentation since the technology of establishing a relationship between gene expression and a phenotype is an empirical and unpredictable technology. This is a critical feature of the claimed invention, and a significant lack of disclosure. Complete reasoning for maintaining the rejection is given in the rejection.

Applicant argues on page 26 that the nexus of the invention is the fact that the gene is identified as differentially expressed, not the nature of the expression, and the nature of the expression is not required to practice the claims. However, this is not persuasive, as discussed in the rejection, and the previous arguments, since the claims are require comparisons with control values that are not disclosed and which cannot be predicted based on the teachings of the prior art.

On page 27 applicant states that methods and protocols for applying differentially expressed genes to indicate the presence of a disease or condition regardless of direction of

change of expression are well established. Applicant cites Slonim who states that the most basic question one can ask is which genes expression levels change significantly. It is a misrepresentation of this reference to suggest that Slonim suggests that methods of classification of individuals can and should be practiced without knowledge of the nature of the expression of a target gene. While Slonim does state that the most basic question is which genes expression levels changes, she also discusses at length that this itself is a complicated question. Here, the instant claims are drawn to making a classification of an individual based on the expression of a single gene. All of the methods for classification discussed by Slonim rely on inputted data regarding the exact nature of the change in expression. Slonim teaches that often classification of the a training set may be perfect, but subsequent attempts to classify new test data fail dismally, pointing out that sample prediction from array data is particularly challenging (p. 506).

Applicant reiterates that the declaration discloses results that demonstrate that the average level of CRTAM-encoded RAN in blood samples from 19 CAD patients was 2.9 fold higher than that of 14 healthy control subjects, and that this difference is inherent, and need not be expressly set forth in the specification or the claims to enable the claims (page 28). However, the rejection is maintained, even in light of the declaration due to the highly unpredictable nature of this technology, as discussed in the rejection. The instant specification fails to provide a critical piece of information with regard to understanding the relationship between CRTAM expression and CAD. The specification invites one of skill in the art to undertake experimentation to (a) determine the relationship between CAD and CRTAM expression and then to validate that relationship. There is a fundamental absence of information given in the specification. The declaration demonstrates that CRTAM has significantly higher expression in CAD patients, but

this does not make up for the deficiency in the specification. The claims all set forth comparing the test level to "a quantified level of RNA encoded by said gene in blood samples from control subjects..." but the specification does not provide this quantified level, or any quantified level. So, it is left to one of skill in the art to establish what is critical for the practice of the invention. While the specification may rely on the state of the prior art to help enable the invention, the specification may not rely on the state of prior art to supplement what is critical to the practice of the invention- in this case the quantified levels of control RNA encoded by the gene in the control subjects, no matter which type of control subjects. The data given in the declaration is not commensurate in scope with the data given in the specification.

Applicant states that the experimental results disclosed in the declaration merely validate the teachings of the specification, but this is not accurate. The add to the teachings in the specification since they teach that CRTAM RNA have been experimentally shown to be significantly higher in CAD patients relative to healthy controls. The claims all rely on comparison to CRTAM quantified levels that are not given in the specification.

Regarding the discussion of the unpredictability of the technology area, applicant reiterates points that have been previously made in the present remarks or were made and addressed prior to the final office action (remarks pages 28-32). Applicant's point that the fact that CTRAM might be an indicator of other diseases as well has been considered, and this aspect of the rejection has been withdrawn.

Applicant states that the examiner appears to be asking the Applicant to enable a "gold standard" diagnostic test. The examiner is not asking such, but instead is pointing out the deficiencies in the level of teachings given in the specification in order to enable any level of

diagnostic test or test directed at even suggesting that CAD is present. In this case, there is no external validation given in the specification, critical data regarding the relationship between the gene expression activity in diseased versus healthy individuals is absent, and the technology area is highly unpredictableto name a few problems. The examiner is not, and has not required a test with a sensitivity of 100%, contrary to applicant's suggestions.

Having carefully considered all of the remarks, the rejection is maintained.

5. No claim is allowed.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C Switzer whose telephone number is (571) 272-0753. The examiner can normally be reached on Tuesday or Wednesday, from 10:00 AM until 4:30 PM, and on Thursday from 12:30 PM until 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached by calling (571) 272-0735.

The fax phone numbers for the organization where this application or proceeding is assigned are (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)272-0507.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Juliet C. Switzer/
Primary Examiner
Art Unit 1634

October 21, 2008